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Modulation of Audiogenic Seizures by Histamine and Adenosine Receptors in the Inferior Colliculus

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Susceptibility to behaviorally similar audiogenic seizures (AGS) occurs genetically and is inducible during ethanol withdrawal (ETX). Comparisons between AGS mechanisms of genetically epilepsy-prone rats (GEPR-9s) and ethanol-withdrawn rats (ETX-Rs) are yielding information about general pathophysiological mechanisms of epileptogenesis. The inferior colliculus (IC) is the AGS initiation site. Excitatory amino acid (EAA) abnormalities in the IC are implicated in AGS, and histamine and adenosine receptor activation each reduce EAA release and inhibit several seizure types. Previous studies indicate that focal infusion of an adenosine receptor agonist into the IC blocked AGS in GEPR-9s, but the effects of adenosine receptor activation in the IC on AGS in ETX-Rs are unknown. The effects of histamine receptor activation on either form of AGS are also unexamined. The present study evaluated effects of histamine or a nonselective adenosine A_1 agonist, 2-chloroadenosine, on AGS by focal microinjection into the IC. Ethanol dependence and AGS susceptibility were induced in normal rats by intragastric ethanol. Histamine (40 or 60 nmol/side) significantly reduced AGS in GEPR-9s, but histamine in doses up to 120 nmol/side did not affect AGS in ETX-Rs. 2-Chloroadenosine (5 or 10 nmol/side) did not affect AGS in ETX-Rs, despite the effectiveness of lower doses of this agent in GEPR-9s reported previously. Thus, histamine and adenosine receptors in the IC modulate AGS of GEPR-9s, but do not modulate ETX-induced AGS. The reasons for this difference may involve the chronicity of AGS susceptibility in GEPR-9s, which may lead to more extensive neuromodulation as compensatory mechanisms to limit the seizures compared to the acute AGS of ETX-Rs. © 2000 Academic Press

Key Words: **audiogenic seizures; genetically epilepsy-prone rats; ethanol withdrawal; inferior colliculus; neuromodulators; histamine; 2-chloroadenosine.**

INTRODUCTION

Generalized seizures can be evoked in response to intense acoustic stimulation chronically in certain rodent genetic strains and are inducible temporarily during ethanol withdrawal (ETX) in otherwise normal rodents. Genetically epilepsy-prone rats (GEPR-9s) and ethanol withdrawn rats (ETX-Rs) both exhibit audiogenic seizures (AGS), and both of these AGS models are being used to examine the mechanisms of generalized epilepsy. AGS in GEPR-9s are characterized by tonic seizures culminating in tonic hindlimb extension. ETX-Rs exhibit AGS composed of a wild running episode which is sometimes followed by clonus and/or tonus. Tonic hindlimb extension is rarely observed in ETX-Rs. Glutamatergic and GABAergic neurotransmitter abnormalities in the brain are proposed to be major factors in both forms of AGS (23, 60). Thus, the effectiveness of GABA-mediated inhibition is decreased during ETX (44; 53, 54, 59), and excitant amino acid-mediated excitatory neurotransmission is enhanced during ETX (11, 21, 31, 40, 51, 55, 68, 72). AGS susceptibility in GEPR-9s is also associated with a deficiency of GABA-mediated inhibition (22, 24, 26, 39) and an excess of glutamate action (9, 30, 61).

The inferior colliculus (IC) is an important midbrain nucleus for processing auditory information (6) and plays a critical role in AGS initiation in AGS in GEPR-9s and in ETX-Rs (31). The IC is very sensitive to blockade of AGS susceptibility in GEPR-9s by a variety of agents, including GABA receptor agonists (5, 27) and NMDA receptor antagonists (30, 50). Both auditory-evoked neuronal responses and spontaneous neuronal firing were greatly enhanced in the IC of GEPR-9s, particularly at high acoustic intensities (29). Tonic neuronal firing in the IC of GEPR-9s was observed just prior to the beginning of AGS (23). All these findings support a major role for the IC in AGS initiation in GEPR-9s. Similar results were also found in ETX-Rs. GABA agonists or *N*-methyl-D-aspartate (NMDA) antagonists microinfused into the IC reduced AGS susceptibility in ETX-Rs (37, 38, 60). Elevated neuronal firing in the IC during ETX was associated with AGS susceptibility (8, 32). AGS-like behaviors could also be induced by electric stimulation of the IC in normal rats (49).

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Adenosine and histamine are two endogenous neuroactive substances known to modulate seizure susceptibility (1–3, 7, 15, 34, 43, 52, 67, 74, 76). Receptors for both of these neuromodulators are present in many brain structures, including the IC (57, 73). Both of these neuromodulators are reported to decrease the release of glutamate (4, 17, 33, 36). Microinjection of a nonselective adenosine A_1 receptor agonist, 2-chloroadenosine, into the IC has been shown to reduce AGS severity in GEPR-9s (16), but the effect of adenosine receptors on AGS in ETX-Rs is unknown. The effect of histamine on AGS in either GEPR-9s or ETX-Rs has not been examined. Therefore, in this study, we microinjected histamine or 2-chloroadenosine into the IC to evaluate whether these agents modulate AGS in GEPR-9s or ETX-Rs. Preliminary results of this study have been reported (25).

METHODS

The colony of severe strain of genetically epilepsy-prone rats (GEPR-9s; 300–400 g) used in these experiments originated from the University of Illinois and were subsequently bred at our animal facility. Normal Sprague–Dawley (SD) rats, the strain from which the GEPR-9s were derived, weighing 300–400 g, were used for ethanol dependence experiments. The animals were housed in a light- and temperature-controlled animal facility prior to the experiments with free access to water and food. AGS susceptibility in both GEPR-9s and ETX-Rs was examined in a sound-attenuating chamber in which an electric bell was mounted. The animals were exposed to the bell (122 dB SPL, re: 0.0002 dyn/cm^2, broad-spectrum acoustic stimulus) until the onset of seizures or for a maximum of 60 s, and the seizure behaviors were recorded on videotape. The severity of seizures in GEPR-9s was scored from 0 to 9 (42). The AGS in ETX-Rs were evaluated by the incidence of the following behaviors: wild running (WR), clonus (C), and tonus (T) (60).

Ethanol dependence was induced in normal rats by intragastric intubation of ethanol solution (47). Ethanol (95%) was diluted with water to form a 30% (v/v) ethanol solution, in which 5 ml of low-iron infant formula (Similac, Ross Products Division, Abbott Laboratories, Columbus, OH) was added to compensate for the ethanol-induced decrease in food intake. The animals also had free access to food and water during ethanol administration. Initially, each animal was given a dose of 5 g/kg of ethanol solution, and each subsequent dose was based on the animals' behavior to maintain the intoxication of the rats at the mild to moderate ataxic state, as described by Majchrowicz (47). The animals were given the ethanol solution every 8 h for 4 days and ethanol was withdrawn at the end of fourth day.

GEPR-9s and normal SD rats were anesthetized with ketamine/xylazine (85/3 mg/kg, ip). A hole was drilled bilaterally in the calvarium over the IC (9.3 mm posterior to bregma, ±1.5 mm medial/lateral, −4.5 mm vertical from surface of the brain) (58). Guide cannulae (21 gauge) were implanted over cortex and affixed onto the rat skull by dental acrylic. During the 7-day recovery period, the animals were given tetracycline (1 g/liter) in the drinking water to reduce the chances of infection. One week after surgery, the GEPR-9s were tested to verify AGS susceptibility. The AGS susceptibility of ETX-Rs was tested starting at 19 h postwithdrawal (60). Only the animals exhibiting AGS were used for microinjection. Vehicle (normal saline) was infused at 0.25 μl/min for 2 min using a Hamilton syringe and a Harvard infusion pump. The AGS susceptibility of the animals was confirmed 15 min later. If vehicle infusion did not alter the AGS susceptibility, histamine or 2-chloroadenosine (RBI, Natick, MA) dissolved in saline was infused into the IC for 2 min at 0.25 μl/min following the AGS testing. The AGS susceptibility of the animals was tested at 30 min and 1, 2, and 4 h after infusion and until recovery in GEPR-9s, and no consistent change in seizure pattern was observed in either GEPR-9s or ETX-Rs due to the repeated testing in the present study or in previous studies (27, 60).

At the end of the experiment, the animals were deeply anesthetized with pentobarbital (100 mg/kg) and perfused with normal saline and 10% formalin. The brains were removed and preserved in formalin. Sections of brain (40 μm) were sliced on a freezing microtome and stained with neutral red. The tracks of infusion cannulae were identified microscopically. The Friedman test was used to analyze statistically the time-course results, and paired t test was used as post hoc analysis to compare the AGS score at each time point with that at vehicle control. Kruskal–Wallis test was used to evaluate the dose–response relationships. Every effort was made to ease any discomfort of the animals utilized in these experiments, and experimental protocols were approved by institutional and National Institutes of Health review committees.

RESULTS

The distribution of representative microinjection sites in the IC is shown in Fig. 1, and the sites were localized to the central nucleus of the IC in both GEPR-9s and ETX-Rs. Analysis of the results (Fig. 2) indicates that both the 40 and the 60 nmol/side doses of histamine microinjected into the IC significantly reduced the AGS severity in GEPR-9s ($P < 0.01$, Friedman test). With both the 40- and the 60-nmol doses, AGS susceptibility was suppressed significantly at 30 min after histamine infusion, and AGS were totally blocked 24 h ($P < 0.01$, paired t test) after drug administration. The degree of AGS suppression of the 60-nmol dose of histamine was not significantly greater

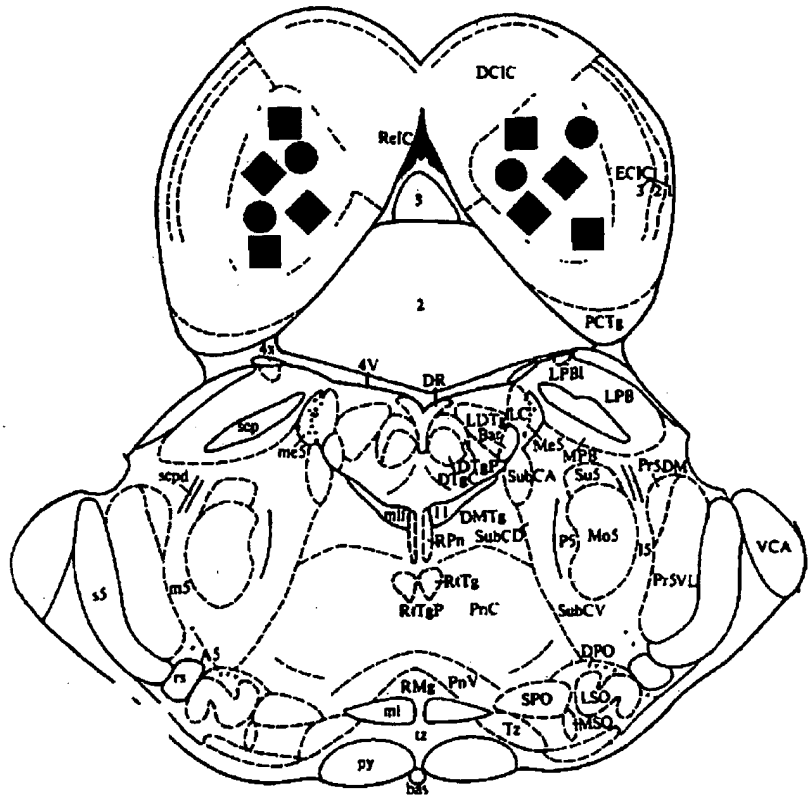

FIG. 1. Representative sites for bilateral microinjection of histamine into the inferior colliculus of GEPR-9s (squares) and ETX-Rs (circles) or 2-chloroadenosine into the inferior colliculus of ETX-Rs (diamonds). All sites were localized to the central nucleus of inferior colliculus, according to the atlas of Paxinos and Watson (58).

in magnitude than that of the 40-nmol dose (Kruskal–Wallis test). Susceptibility to AGS in GEPR-9s returned at 120 h after infusion of the 40-nmol dose of histamine, but AGS susceptibility was still significantly suppressed in GEPR-9s that had received the 60-nmol dose, indicating the effect of the 60-nmol dose of histamine lasted longer than that of the 40-nmol dose (Fig. 2). Recovery from the 60-nmol dose of histamine was observed by 216 h after drug infusion.

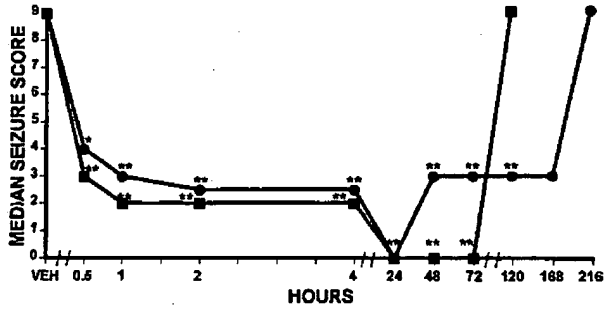

FIG. 2. Time course of the effects of histamine on the audiogenic seizures (AGS) in the severe strain of genetically epilepsy-prone rats (GEPR-9s) after bilateral microinjection into the inferior colliculus (IC). The anticonvulsant effect of histamine began 0.5 h and reached a maximum 24 h after microinjection. The squares represent 40 nmol/side ($N = 7$) and the circles represent 60 nmol/side ($N = 6$) of histamine. * Significantly different from predrug vehicle (VEH) control at $P < 0.05$. ** Significantly different from predrug VEH control at $P < 0.01$ (paired t test).

Susceptibility to AGS was examined beginning 19 h after the ethanol was withdrawn. Of all the 32 animals utilized in the ETX experiments, WR during AGS was observed in all ETX-Rs. C was exhibited in 21 ETX-Rs (Fig. 3), and only 7 ETX-Rs showed T. The incidence of T was not sufficient to allow statistical evaluation. In those ETX-Rs exhibiting WR and C, histamine (60 or 120 nmol) microinjected into the IC failed to exert a significant effect on the incidence of these behaviors at 0.5, 1, 2, and 4 h after histamine microinjection. Although 2-chloroadenosine produced a trend toward reduction of C incidence, this effect was not statistically significant. Thus, neither 5 nor 10 nmol of 2-chloroadenosine exerted significant anticonvulsant effect on WR in ETX-Rs at 0.5 to 4 h after drug infusion, which contrasts with previously published data in GEPR-9s (16). The effects of these two neuromodulators on AGS component incidence in ETX-Rs at 1 h postinfusion are shown in Fig. 3.

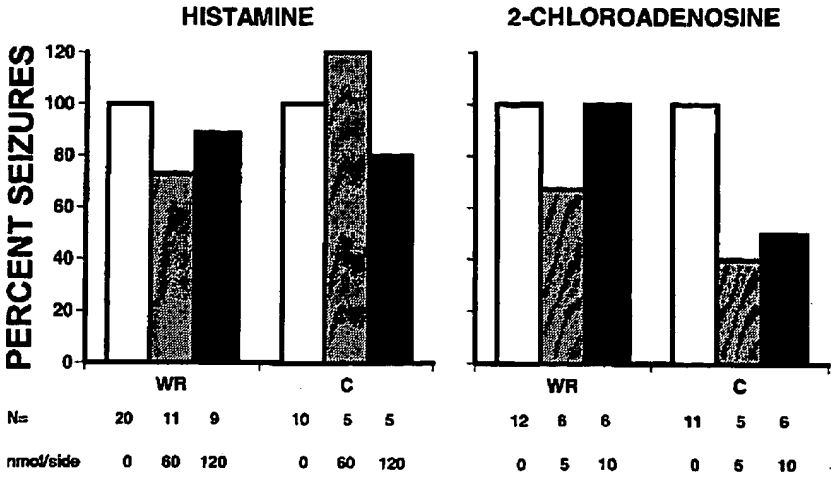

FIG. 3. Effects of microinjection of different doses of histamine or 2-chloroadenosine into the inferior colliculus (IC) on the percentage of wild running (WR) or clonus (C) 1 h after drug infusion in ethanol withdrawn rats (ETX-Rs). The number of animals exhibiting these AGS behaviors during vehicle control was considered a 100% response. The zero dose represents predrug vehicle control. N, number of animals exhibiting WR or C in each case. No significant changes were observed.

DISCUSSION

The present study indicates that microinjection of histamine into the IC significantly reduces AGS susceptibility in GEPR-9s, suggesting that histamine plays a role in modulating the AGS in the IC of these animals. The 60 nmol/side of histamine exerted a longer duration of anticonvulsant effect than the 40-nmol dose. Although the magnitude of effects of these two doses was not significantly different, for reasons that are not entirely clear, one possibility is that the histamine receptors in the IC were completely occupied at the 40-nmol dose. The long duration of histamine action in the current study is in accord with a previous study in which metoprine, a drug that blocks histamine methylation, significantly suppressed seizures at 28 h after drug administration in another strain of the AGS-susceptible rats (70). A recent study in our lab also observed a long-lasting effect of histamine on inhibition of seizures in GEPR-9s (34). The reasons for the delay in maximal effect of histamine are unclear. Histamine receptor activation stimulates multiple second messenger systems (46). Histamine can directly activate adenylate cyclase and elevate intracellular cAMP level, which has been shown to exert an anticonvulsant effect (35). Histamine also potentiates the effect of adenosine on stimulation of adenylate cyclase (14). Histamine inhibits the release of glutamate via activating presynaptic H_3 receptors (4). The activity of histamine metabolic enzymes was found to be lower in AGS-susceptible rodents (19). Each of these actions may contribute to the delayed maximal response of histamine on AGS in GEPR-9s.

In the present study, neither histamine nor 2-chloroadenosine microinjection into the IC was effective in suppressing seizures in ETX-Rs. On the other hand, both agents were effective in the GEPR-9s in this and a previous study (16). Previous microinjection studies using competitive NMDA antagonists or $GABA_A$ agonists indicate that an equivalent dose or, at most, twice the dose is required to achieve anticonvulsant effect in the IC of ETX-Rs compared to GEPR-9s (27, 30, 38, 60). In this study, we used 2-chloroadenosine up to 10 nmol, which is reaching the solubility limit of this agent in saline, which is more than six times the dose that totally blocked AGS in the IC of GEPR-9s (16). We also utilized histamine up to 120 nmol, which is at least three times the effective dose in GEPR-9s. We did not use higher than 120 nmol doses of histamine, since drugs in very high concentrations could affect the function of nuclei beyond the IC due to volume transmission (78). Thus, doses up to three to six times the dose of histamine or 2-chloroadenosine effective in GEPR-9s were ineffective in ETX-Rs at any time point examined. In the present study, we observed that the anticonvulsant effect of histamine reached maximum at 24 h after drug infusion in GEPR-9s. Therefore, in preliminary experiments, we microinjected histamine 60 or 120 nmol/side bilaterally into the IC of ETX-Rs 24 h before they became susceptible to AGS and found that histamine administration also failed to exert any anticonvulsant effect on the subsequent AGS.

The anticonvulsant effects of histamine and 2-chloroadenosine in GEPR-9s observed in the current and a previous study (16) may be due, in part, to actions of these agents on excitatory amino acid (EAA) action. Presynaptic adenosine A_1 receptor activation inhibits the release of glutamate (17, 33, 36), which was proposed to be the mechanism of anticonvulsant effect of

adenosine agonists in the IC of GEPR-9s (16). Histamine presynaptic H_3 receptor activation also leads to suppression of glutamate release (4). Significant changes in EAA neurotransmission have been observed in the IC of GEPR-9s (9, 61). Microinjection into the IC of agents that block NMDA receptors or glutamate synthesis blocked the AGS susceptibility in GEPR-9s (28, 30, 50), suggesting that enhanced glutamatergic neurotransmission is a critical factor for seizure susceptibility in GEPR-9s. Modulation of glutamate neurotransmission may be one mechanism by which histamine exerts anticonvulsant effects in the IC of GEPR-9s, and H_1 receptor activation may also contribute to this anticonvulsant effect (52, 66, 74–76). Agents that directly block glutamate receptors are effective in suppressing AGS (28, 30, 50). Unfortunately, these agents produce significant side effects, which diminish their therapeutic usefulness (45, 65). Those agents that indirectly modulate the function of glutamate neurotransmission, such as histamine and adenosine receptor agonists, may be more promising therapeutic agents.

The contrasting effects of histamine and 2-chloroadenosine in GEPR-9s versus ETX-Rs observed in the IC in the present and a previous study (16) may reflect pathophysiological differences between the chronic AGS susceptibility in GEPR-9s and the acute nature of AGS susceptibility in ETX-Rs. Glutamatergic, GABAergic, noradrenergic, and serotonergic abnormalities, which modulate AGS susceptibility, have all been observed in GEPR-9s (9, 12, 13, 22, 26, 39, 41, 61–64). The present findings and a previous report (16) also implicate histaminergic and purinergic receptor modulation of seizure suppression in GEPR-9s. This is consistent with histaminergic and purinergic deficiencies observed in several chronic seizure types, including other forms of AGS (18, 20, 56, 69, 71, 77). Such an extensive array of neuromodulatory mechanisms may become involved, in part, in order to compensate for repeated seizure experiences of GEPR-9s, whereas, in ETX-Rs, the duration of AGS susceptibility is transient, and such neuromodulatory mechanisms may not be called into play to compensate for the acute seizure susceptibility. This may account for the lack of effect on AGS in ETX-Rs of exogenous histamine or 2-chloroadenosine in the IC. However, systemic administration of adenosine receptor agonists was reported to antagonize AGS in ETX-Rs (10, 48), suggesting that these agents may exert anticonvulsant effects in structures of the neuronal network for seizures at nuclei beyond the IC. The disparity between effects of microinjection versus systemic administration of the same agents in ETX-Rs is not uncommon. Microinjection of dizocilpine (MK-801), an uncompetitive NMDA receptor antagonist, into IC was relatively ineffective in blocking AGS in ETX-Rs unless excessive doses were utilized, but this agent was very potent with systemic administration (30). On the other hand, microinfusion of MK-801 into a nucleus beyond the IC (the pontine reticular formation) was effective in doses that were ineffective in the IC in blocking AGS in ETX-Rs (60). Such differences in the site of action within the seizure network may also occur with histamine or 2-chloroadenosine. Thus, the present study suggests that histamine and adenosine receptors in the IC of GEPR-9s modulate AGS, but these two agents may be unimportant in modulating AGS in ETX seizures in the AGS initiation site. The reasons for this discrepancy may be due to the chronic nature of AGS susceptibility in GEPR-9s, which contrasts with the acute nature of seizure susceptibility in ETX.

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